学位論文

「**Changes in estimate glomerular filtration rate associated with long-term Tyrosine Kinase Inhibitor treatment in patients with chronic myelogenous leukemia**」

（慢性骨髄性白血病患者におけるチロシンキナーゼ阻害薬の長期使用に関連した推定糸球体濾過率の変化）

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## 著者の宣言

本学位論文は、著者の責任において実験を遂行し、得られた真実の結果に基づいて正確に作成したものに相違ないことをここに宣言する。

【Abstract】

**Objective:** Tyrosine kinase inhibitors (TKIs) have dramatically improved prognosis of chronic myelogenous leukemia (CML), and four kinds of TKIs are currently used for first-line treatment in Japan. Renal damage has been known as a major adverse effect of TKIs, but there are a few reports that describe frequency of renal damage induced by long-term administration of TKIs. Therefore, we retrospectively analyzed the incidence of renal dysfunction with a long-term use of TKIs.

**Methods:** Newly diagnosed 83 CML patients in chronic phase who were treated with TKIs for more than 3 years were analyzed; 54 patients were treated with imatinib, 21 with dasatinib, and 8 with nilotinib. We examined chronological changes of the value of estimated glomerular filtration rate (eGFR) during TKI therapies. The value of eGFR was calculated using the Japanese Association of Chronic Kidney Disease Initiatives (J-CKDI).

**Results:** The median follow-up duration was 10.3 years in the imatinib, 5.45 years in the dasatinib and 6.66 years in the nilotinib cohort. Imatinib was associated with higher incidence of renal dysfunction compared to dasatinib and nilotinib ($P=0.0061$). After five years of treatment, reduction in the mean value of eGFR ($mL/min/1.73m^2$) in the imatinib, dasatinib, and nilotinib groups were 20.22 ($p<0.0001$), 10.26 ($p=0.0026$), and 2.667 ($p=0.3105$), respectively. Multivariate analyses revealed that treatment with imatinib and female gender were the significant risk factors for renal damage.

**Conclusion:** Long-term use of imatinib was significantly correlated with development of drug-induced renal damage compared with dasatinib and nilotinib.

目次

## 1. Introduction

Chronic myelogenous leukemia (CML) is a type of myeloproliferative neoplasm characterized by an abnormal fusion gene *BCR-ABL1*. The fusion gene is generated by a chromosomal translocation t(9;22)(q34.1;q11.2), and a newly formed chromosome is called Philadelphia (Ph) chromosome. The gene product of *BCR-ABL1* is a tyrosine kinase with an increased kinase activity and plays central roles in the pathogenesis of CML [1]. Tyrosine kinase inhibitors (TKIs) have dramatically improved prognosis of CML, and they are currently used as standard first-line drugs [2]. Imatinib mesylate (IMA) was the first TKI to be successfully used in the treatment of CML. IMA binds to the ATP-binding pocket of the BCR-ABL1 kinase, and it inhibits tyrosine kinase activity of the molecule [3, 4]. IMA is generally well tolerated with fewer adverse events (AEs) than those with traditional cytotoxic agents, *e.g.* cytarabine, interferons, hydroxyurea and busulfan.

Currently, second-generation TKIs, *i.e.* nilotinib hydrochloride (NIL), dasatinib hydrate (DAS) and bosutinib hydrate (BOS), have been developed, and these TKIs demonstrate efficacy even in cases with resistance or intolerance to IMA [5-7]. All of the TKIs are designed to inhibit ABL1 tyrosine kinase [8], but they have certain levels of off-target inhibitory effects on other kinases, *e.g.* PDGFR-α, PDGFR-β, c-kit, Src, DDR-1, DDR-2 [9, 10], and the deference in the off-target profiles is supposed to be related to the difference in the AEs of each TKI.

Among these AEs, renal damage has been reported in several studies [7, 11-16]. These studies describe that TKIs may reduce estimated glomerular filtration rate (eGFR), and the AEs is more distinct in IMA than in other TKIs [12-15]. Since PDGFR is widely expressed on renal cells, and PDGFR plays important roles in tubular cell regeneration [17-19], the renal adverse effects may be induced by the off-target inhibition of PDGFR by TKIs interfering with renal repairments. Cancers and anti-cancer therapies often affect renal function, and understanding how kidneys react in the oncologic background is important for the treatment of cancers; this field of science is now attracting attention as onco-nephrology.

Treatment with TKIs has enabled CML patients to survive for a long time. Therefore, it is most important to clarify long-term effects of TKIs on kidney function. Currently, four TKI drugs, IMA, NIL, DAS and BOS, can be used as the first-line drugs [20], but long-term effects of these TKIs on renal functions have not been fully understood [13]. Therefore, to elucidate the long-term effects of TKIs on renal functions, we retrospectively analyzed data of CML patients who were treated with IMA, NIL and DAS, and we evaluated the long-term clinical outcomes in renal functions of these patients.

## 2. Materials and methods

### *2-1. Patients and study design*

Medical records of 136 consecutive adult CML-chronic phase (CP) patients who received IMA (Glivec®), NIL (Tasigna®), or DAS (Sprycel®) as the first line TKI treatment at Kitasato University hospital between January 2001 and December 2018 were retrospectively reviewed. All the patients were diagnosed with CML with the presence of either Ph chromosome or *BCR-ABL1* transcripts in the peripheral blood or bone marrow cells. In the analyses, patients with eGFR ≤29 mL/min/1.73 $m^2$, in the accelerated phase (AP) or blast phase (BP) at the point of therapy initiation were excluded. Patients who had nephrectomy were also excluded. To evaluate long-term AE profiles of the drugs, patients who were treated with TKIs for less than 3 years were also excluded in this study.

The primary end point of the study was eGFR changes in the clinical course. Secondary end point was renal event-free survival (renal EFS); a renal event was defined as 20 mL/min/1.73 $m^2$ of reduction of eGFR from the baseline, and renal EFS was defined as the duration from the initiation of the TKI treatment to the onset of a renal event.

Observation of the patients was censored when the first line TKI was stopped or switched to another TKI, or patients were dead or dropped out or transferred to other hospitals, or the disease progressed to AP or BC. In this study, values of eGFR were calculated using the 3-variable Japanese equation, proposed by Japanese Association of Chronic Kidney Disease

Initiatives (J-CKDI): eGFR (mL/min/1.73 $m^2$) = 194 × Serum creatinine$^{-1.094}$ × Age$^{-0.287}$ × 0.739 (if female) [21]. Since urinalytic data were lacking in many cases, renal damage was evaluated by blood tests, *i.e.* eGFR.

This study was performed as a clinical study under the approval of the ethical committee of Kitasato University Hospital (B18-287).

### *2-2. Statistical analyses*

Kruskal-Wallis and Mann-Whitney tests were used to evaluate statistical difference between each TKI group. Paired t-test was used to assess the difference of mean eGFR between baseline and each time point. We plotted event free survival curves using Kaplan-Meier estimates. Log-rank tests were used to analyze survival data. Univariate and multivariate Cox proportional hazard models were used to identify the factors that are associated with development of renal dysfunction. P-values of $<0.05$ were considered statistically significant.

Statistical analyses were performed by using Prism software (version 8.4.3, GraphPad software, San Diego, CA), and univariate and multivariate analyses were performed using StatMate software (version 5.01, ATMS Co., Ltd).

## 3. Result

### *3-1. Patient characteristics*

Available data on 136 patients were reviewed, and 53 patients were excluded from the analyses with following reasons: post-nephrectomy (n=2), eGFR ≤29 mL/min/1.73 $m^2$ (n=1), and less than 3 years of treatment with TKIs (n=50) (Figure 1).

As a result, a total of 83 CML-CP patients were enrolled; 54 patients were treated with IMA, 21 with DAS and 8 with NIL as the first-line therapy (Figure 1). Patient characteristics are summarized in Table 1. In the IMA cohort, the median duration of observation was 123.7 months (range: 40-203 months), 52% were males, and median age was 53.3 years (range: 24-89 years). The baseline median eGFR level was 84.2 mL/min/1.73 $m^2$ (range: 43.8-130.2 mL/min/1.73 $m^2$). In the DAS cohort, the median duration of

observation was 65.4 months (range: 37-114 months), 57% were males, and median age was 57.8 years (range: 29-80 years). The baseline median eGFR level was 72.1 mL/min/1.73 $m^2$ (range: 48.2-100 mL/min/1.73 $m^2$). In the NIL cohort, the median duration of observation was 79.9 months (range: 60-93 months), 75% were males, and median age was 54.4 years (range 19-74 years). The baseline median eGFR level was 72.8 mL/min/1.73$m^2$ (range: 31-107.8 mL/min/1.73$m^2$). Patient characteristics, *i.e.* age, gender and median baseline eGFR levels were not significantly different between these cohorts. Medical comorbidities, *i.e.* hypertension, diabetes mellitus and hyperlipidemia, in these cohorts were also similar, but duration of TKI treatment was significantly longer in the IMA cohort (P <0.0001) (Table1).

### *3-2. Changes in eGFR values in each TKI cohort*

At first, we analyzed changes of eGFR in each TKI cohort. As a result, mean eGFR in the IMA and DAS cohorts showed gradual decrease, but eGFR in the NIL cohort remained stable. In the IMA cohort, eGFR levels were significantly reduced in all observation periods compared with the baseline (P<0.0001), with a mean eGFR reduction after 5 years of treatment was 20.22 mL/min/1.73$m^2$ (p<0.0001) (Figure 2A). In the DAS cohort, the mean value of eGFR reduction after 5 years was 10.26 mL/min/1.73$m^2$ (p=0.0026). Reduction of eGFR values was more prominent in the IMA cohort compared with the DAS cohort. On the other hand, eGFR levels in patients treated with NIL did not change significantly, and the mean reduction at the point of 5 years was 2.67 mL/min/1.73$m^2$ (p=0.3105).

Next, to evaluate the impact of pre-treatment renal function on the post-treatment renal outcome, we analyzed changes of eGFR in patients with normal (eGFR ≥60 mL/min/1.73$m^2$) (Figure 2B) or impaired (eGFR <60 mL/min/1.73$m^2$) (Figure 2C) renal function at baseline.

Figure 2B shows the renal outcomes in patients with normal renal function at baseline. In these patients, treatment with IMA and DAS reduced eGFR levels significantly (P<0.0001 and P<0.001, respectively), but treatment with NIL did not show significant reduction. The mean eGFR

reduction from baseline after 5 years of treatment in the IMA, DAS, and NIL cohorts was 21.75, 11.9, 4.25 mL/min/1.73m$^2$, respectively.

On the other hand, in patients with impaired renal function at the initiation of TKI treatment, reduction of eGFR was less pronounced than that observed in patients with normal renal function, and significant reduction was observed only in patients treated with IMA (P<0.01) (Figure 2C). Treatment with NIL did not show obvious reduction of eGFR. The mean eGFR changes from the baseline after 5 years in the IMA, DAS, and NIL cohorts was -9.28, -5.9, and +0.5 mL/min/1.73m$^2$, respectively (Figure 2C). Characteristics of the patients with impaired renal function at baseline were almost similar among all three TKI cohorts (Table 2).

### *3-3. Renal event free survival in each TKI cohort*

To evaluate the onset and factors that affect TKI-induced renal damage, we analyzed renal EFS in patients treated with TKIs. In the analyses, we defined a renal event as 20mL/min/1.73m$^2$ reduction of eGFR. As a result, median renal EFS in the IMA, DAS, and NIL cohorts was 3.91 years, 6.67 years, and not reached, respectively, and significant difference was found between these TKI cohorts (P=0.0061) (Figure 3). These results indicate that treatment with IMA is related to a higher risk of early renal dysfunction.

Next, to evaluate clinical factors associated with TKI-induced renal events, we performed univariate and multivariate analyses (Table 3). Univariate analysis showed that normal renal function at baseline was the primary risk factor for renal damage with a hazard ratio (HR) of 4.57 (95%CI 1.42-14.7; P<0.05). Treatment with IMA and female gender were the secondary risk factors with HRs of 2.69 and 2.47, respectively (95%CI 1.30-5.58; P<0.01, and 95%CI 1.40-4.38; P<0.01). In the multivariate analysis, treatment with IMA and female gender remained significant as risk factors for the development of renal damage, and HRs were 2.34 and 2.46 (95%CI 1.12-4.87; P<0.05, 95%CI 1.34-4.51; P<0.05), respectively. Notably, multivariate analysis showed that normal renal function at baseline showed a high risk of renal damage with a HR of 3.22, but the association had no statistical significance (95%CI 0.96-10.81; P=0.058). This

might be partly due to a bias in the number of patients; the number of patients with impaired and normal renal function at baseline was 14 and 69, respectively.

### *3-4. Renal dysfunction in patients treated with IMA*

Our data showed that treatment with IMA was associated with a higher risk of renal damage. Therefore, we evaluated clinical factors that affect renal damage in the patients treated with IMA. Renal EFS stratified with renal function at baseline showed that normal renal function at baseline was a significant factor for a shorter EFS with a HR of 3.25 (95%CI 1.54-6.88, $P<0.05$) (Figure 4A). Median EFS in patients with normal and impaired renal function at baseline was 3.58 years and not reached, respectively. In this analysis, female gender was also a significant risk factor for renal AEs; median EFS in female and male patients was 2.96 and 6 years, respectively, with a HR of 1.98 in female (95%CI: 1.07-3.68, $P<0.05$) (Figure 4B). These results show that in patients treated with IMA, renal AEs will be more pronounced in patients with normal renal function and female. Multivariate analysis showed that also in the IMA-treated subgroup, female gender was an independent risk factor for renal damage with a HR of 2.24 (95%CI 1.15-4.37; $P<0.05$) (Table 4). Interestingly, dosages of IMA did not affect development of renal dysfunction; the HR for renal AEs in the group of higher-dose (≥400mg) of IMA treatment over that of lower-dose (<400 mg/day) of IMA treatment was 0.99 (95%CI 0.5-1.96; $P=0.977$). Moreover, the mean dosage of IMA was not significantly different between male and female, or between patients with normal and impaired renal function at baseline (Table 5).

## 4. Discussion

Treatment with TKIs has remarkably prolonged the survival of CML patients, and this means that we have to pay much attention to the potential long-term toxicity of the drugs. Our analyses showed that treatment with IMA or DAS, especially IMA, was more frequently associated with renal AEs than with NIL. In addition, we found that absence of renal impairment

before treatment and female gender might be significant risk factors for developing renal dysfunction. The average rate of eGFR decline with age in the Japanese population has been reported to be 0.36 mL/min/1.73m$^2$ per a year [22]. Compared to the data, five-year eGFR declines of 20.22 mL/min/1.73m$^2$ and 10.26 mL/min/1.73m$^2$ in patients treated with IMA and DAS, respectively, are supposed to be notably high.

In accordance with our results, Yilmaz *et al.* have reported data of 468 patients treated with IMA, NIL and DAS, who had been enrolled into a prospective clinical study [13]. They showed that treatment with IMA, absence of renal dysfunction at baseline, advanced age and history of hypertension or diabetes were significantly related to the development of renal dysfunction.

Molecular mechanisms of renal damage caused by TKIs have not been fully understood. However, a previous report has suggested that the toxic effects of IMA may be related to renal tubular damage and inhibition of PDGFR signaling pathways [23]. It has been shown that PDGFR is mainly expressed on renal tubules and to a lesser extent in the glomerulus, and expression of PDGFR mRNA is enhanced after ischemic renal injury [17]. Furthermore, PDGF β/PDGFR axis could be significantly involved in renal tubular cell regeneration after acute tubular necrosis in animal models [18]. These findings suggest that PDGFR play important roles in the restoration of damaged renal tubules. TKIs inhibit PDGFRα or PDGFRβ as an off-target effect, and it is known that IMA has comparatively strong inhibitory effects on PDGFR; half maximal inhibitory concentration ($IC_{50}$) of IMA to PDGFR, c-KIT, and BCR-ABL1 were 72 nM, 90 nM, and 211 nM, respectively [24]. These results suggest that IMA could induce renal dysfunction by disturbing tubular restoration through PDGFR inhibition. In our study, we found no dose-effects of IMA on the development of renal damage; lower dose (<400 mg/day) and higher dose (≥400mg/day) of IMA induced eGFR reduction similarly. This finding indicates that dosage of IMA did not affect the reduction of eGFR, and we should be aware that even lower dose of IMA could cause renal impairment.

From the viewpoint of off-target inhibition of tyrosine kinases, NIL is

known as a selective TKI for BCR-ABL1 with less off-target effects. Iyoda *et al.* reported that rats with experimental renal disease have less proteinuria and reduced glomerulosclerosis when treated with NIL [25]. This observation is consistent with our observation that patients treated with NIL had little renal damage.

In the present study, we found that female gender was an independent risk factor for TKI-induced renal dysfunction. In accordance with our study, in a previous prospective study by Yilmaz *et al.*, a multivariate analysis revealed that female gender had a tendency for developing renal dysfunction (HR=1.5; 95%CI 0.7-2.9, P=0.288), although the difference was not statistically significant [13], and the data indicate that gender could be an important factor for TKI-induced renal damage. Underling mechanism for this gender difference has not been clarified, and impact of gender difference on TKI-induced renal damage needs further investigation.

Notably, patients with renal dysfunction at baseline showed no significant reduction in eGFR during treatment with DAS or NIL, and just modest decrease with IMA. Yilmaz et al. have also reported similar observation that patients with renal dysfunction at baseline showed less renal damage after treatments with TKIs [13]. This is an interesting finding, but currently, underling mechanism has not been understood.

Although, at this time, we cannot explain clearly why female gender or normal renal function at baseline are independent risk factors for TKI-induced renal damage, it has been reported that trough plasma concentration of TKI is associated with efficacy and toxicity [26]. Recent approval of therapeutic drug monitoring for IMA in Japan has enabled us to monitor drug concentration, and therefore, further investigation on the association of drug concentration and observed risk factors will be needed.

Moreover, it is known that increasing urinary β2-microglobulin (β2-MG) is a predictor for tubular dysfunction. Ren *et al.* reported that patients who developed renal dysfunction after treatment with TKIs had higher urinary β2-MG levels than those who did not [15]. It has been speculated that the gradual increase in urinary β2-MG may be due to TKI-induced tubular damage. It may be meaningful to evaluate the significance of urinary β2-MG

as an early predictor for renal damage in the treatment with TKIs.

In conclusion, our study demonstrated that long-term treatment with IMA and DAS, especially IMA, was significantly associated with renal adverse effects, and we found several associated risk factors. The results strongly suggest that when we administer TKIs for the treatment of CML, we should be aware of the risk of renal damage according to the prescribed TKIs, and monitor eGFR regularly.

## 5. References


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6. Achievement list

（Ⅰ）主学術論文（英文原著）

◎1．Motohashi T, Kamata H, Hayama K, Michishita Y, Horigome Y, Tadera N, Okina S, Suzuki T ：

Changes in estimate glomerular filtration rate associated with long-term Tyrosine Kinase Inhibitor treatment in patients with chronic myelogenous leukemia

The Kitasato Medical Journal VOL. 51 No. 1. in press

(Ⅱ)原　著(主学術論文を除く)

なし

(Ⅲ)著　書

なし

(Ⅳ)総説・講座

なし

(Ⅴ)症例・臨床治験・その他

○1. Ishida T, Miyazaki K, Okina S, Miyata T, Hayama K, Higashihara M, Suzuki T : The clinical outcomes of chronic myeloid leukemia patients harboring alternatively spliced BCR-ABL variants Hematology. 2019 Dec;24(1):49-51.

○2. Ishida T, Akagawa N, Miyata T, Tominaga N, Iizuka T, Higashihara M, Suzuki T, Miyazaki K : Dasatinib-associated reversible demyelinating peripheral polyneuropathy in a case of chronic myeloid leukemia Int J Hematol. 2018 Mar;107(3):373-377.

## 7. Figure legends

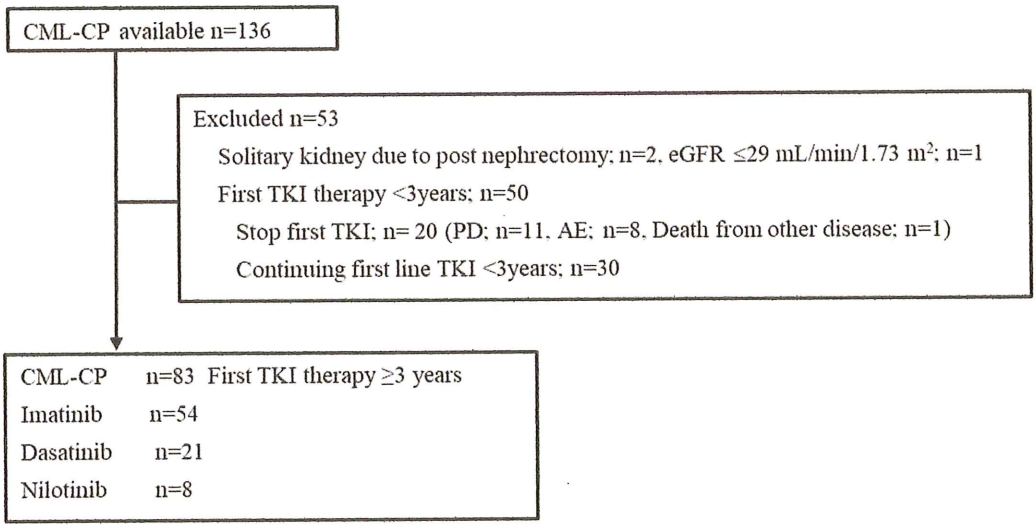


**Figure 1.** Outline of patients in the study.
CML-CP: Chronic myelogenous leukemia in chronic phase, TKI: tyrosine kinase inhibitor,
PD: Progressive disease, AE: Adverse event.

**Table 1.** Clinical characteristics of the patients

| Characteristics | Imatinib (n=54) | Dasatinib (n=21) | Nilotinib (n=8) | P value |
|---|---|---|---|---|
| Age, median (range), years | 53.3 (24-89) | 57.8 (29-80) | 54.4 (19-74) | 0.539 |
| Gender, No. of patients (%) | | | | 0.4662 |
| Male | 28 (52) | 12 (57) | 6 (75) | |
| Female | 26 (48) | 9 (43) | 2 (25) | |
| eGFR, median (range) | 84.2 (43.8-130.2) | 72.1 (48.2-100) | 72.8 (31-107.8) | 0.072 |
| Patients with impaired renal function (eGFR<60) at baseline (%) | 7 (12.9) | 5 (23.8) | 2 (25.0) | 0.9968 |
| Patients of comorbidities (%) | | | | |
| Any comorbidities | 24 (45.2) | 14 (66.7) | 6 (75) | 0.0973 |
| Hypertension | 11 (20.3) | 5 (23.8) | 3 (37.5) | 0.5606 |
| Diabetes Mellitus | 8 (14.8) | 3 (14.3) | 3 (37.5) | 0.3187 |
| Hyperlipidemia | 14 (25.9) | 10 (47.6) | 4 (50) | 0.1237 |
| Median follow up duration (range), month | 123.7 (40-203) | 65.4 (37-114) | 79.9 (60-93) | <0.0001* |

eGFR: estimated glomerular filtration rate.
The data were statistically calculated with Kruskal-Wallis test.
* P value indicated a significant difference.

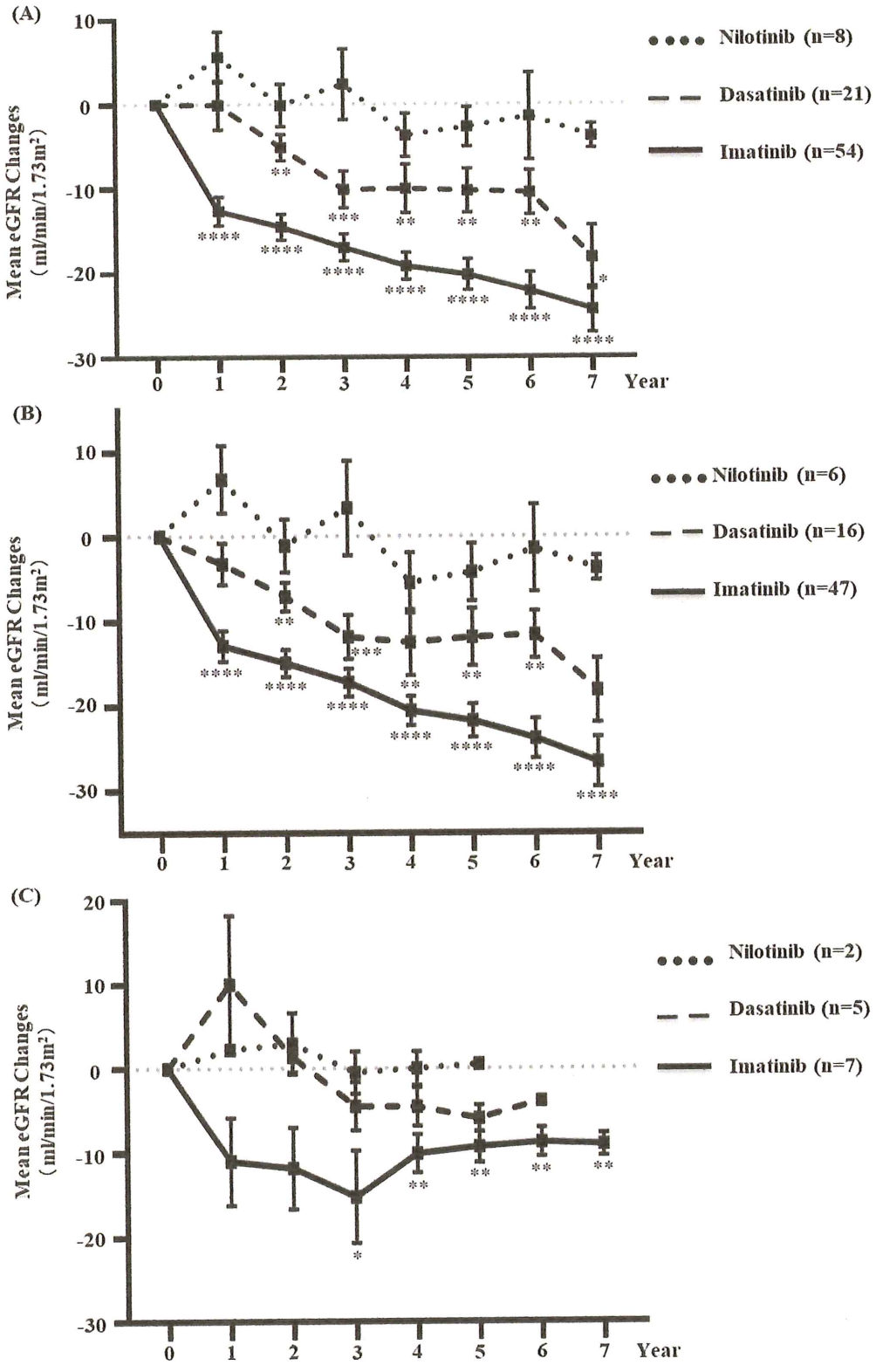
(A)
Mean eGFR Changes (ml/min/1.73m²)
10
0
-10
-20
-30
0 1 2 3 4 5 6 7 Year
Nilotinib (n=8)
Dasatinib (n=21)
Imatinib (n=54)
(B)
Mean eGFR Changes (ml/min/1.73m²)
10
0
-10
-20
-30
0 1 2 3 4 5 6 7 Year
Nilotinib (n=6)
Dasatinib (n=16)
Imatinib (n=47)
(C)
Mean eGFR Changes (ml/min/1.73m²)
20
10
0
-10
-20
-30
0 1 2 3 4 5 6 7 Year
Nilotinib (n=2)
Dasatinib (n=5)
Imatinib (n=7)

**Figure 2.** Mean eGFR changes from baseline

(A) All CML-CP Patients (n=83)

(B) CML-CP Patients with normal renal function at baseline (n=69)

(C) CML-CP Patients with impaired renal function at baseline (n=14)

eGFR: estimated glomerular filtration rate. CML-CP: Chronic myelogenous leukemia in chronic phase.

The data were statistically calculated with paired t-test between the baseline and each time point.

* p<0.05, * * p<0.01, * * * p<0.001, * * * * p<0. 0001.

Table 2. Clinical characteristics of the patients with impaired renal function (eGFR<60ml/min/1.73m$^2$) at baseline

| Characteristics | Imatinib (n=7) | Dasatinib (n=5) | Nilotinib (n=2) | P value |
|---|---|---|---|---|
| Age, median (range), years | 72.1 (58-89) | 66.2 (56-80) | 62 (50-74) | 0.4977 |
| Gender, No. of patients (%) | | | | >0.9999 |
| Male | 6 (85.7) | 4 (80) | 2 (100) | |
| Female | 1 (14.3) | 1 (20) | 0 (0) | |
| eGFR, median (range) | 52.57 (43.8-58.9) | 53.46 (48.2-58.8) | 45 (31-59) | 0.9006 |
| Patients of comorbidities (%) | | | | |
| Any comorbidities | 4 (57.1) | 4 (80) | 2 (100) | 0.4406 |
| Hypertension | 3 (42.9) | 1 (20) | 1 (50) | 0.7902 |
| Diabetes mellitus | 2 (28.6) | 1 (20) | 1 (50) | >0.9999 |
| Hyperlipidemia | 1 (14.3) | 4 (80) | 0 (0) | 0.0385* |
| Median follow up duartion (range), month | 100.4 (55-155) | 64.0 (42-82) | 64.5 (60-69) | 0.1456 |

eGFR: estimated glomerular filtration rate.

The data were statistically calculated with Kruskal-Wallis test.

* P value indicated a significant difference.

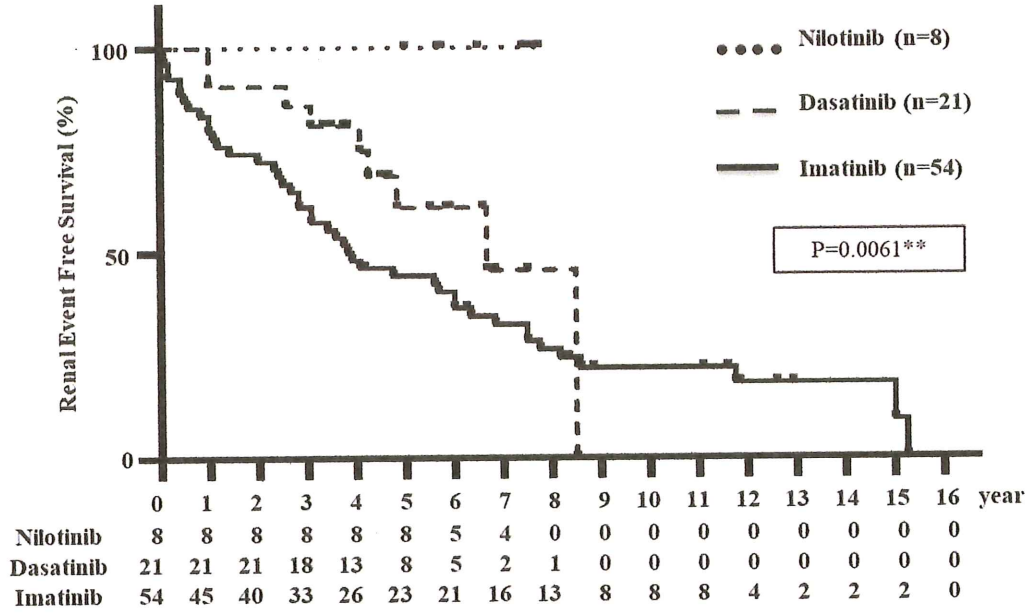


**Figure 3.** Renal EFS in patients with first-line TKI therapy.
Median survival was 3.91 years (47 month) in imatinib, 6.67 years (80 month) in dasatinib, and not reached in nilotinib.
EFS: Event free survival, TKI: tyrosine kinase inhibitor
The data were statistically calculated with Log-rank (Mantel-Cox) test.
* p<0.05, * * p<0.01, * * * p<0.001, * * * * p<0. 0001.

Table 3. Univariate and Multivariate analysis on Renal EFS in patients with TKI therapy

| Variables | Univariate analysis | | Multivate analysis | |
|---|---|---|---|---|
| | HR (95%CI) | P-Value | HR (95%CI) | P-Value |
| Imatinib | 2.6936<br>1.299-5.582 | 0.007698* | 2.336<br>1.1224-4.865 | 0.0232* |
| Normal renal function at baseline (eGFR≥60) | 4.5781<br>1.4232-14.726 | 0.01071* | 3.222<br>0.960-10.811 | 0.058 |
| Age <60 years | 1.4098<br>0.779-2.485 | 0.235 | 1.337<br>0.731-2.444 | 0.3444 |
| Female gender | 2.4733<br>1.3974-4.3775 | 0.0018* | 2.458<br>1.339-4.512 | 0.0036* |
| No comorbidities | 1.526<br>0.8838-2.635 | 0.1292 | 1.563<br>0.881-2.771 | 0.126 |

EFS: Event free survival, TKI: Tyrosine kinase inhibitor,
eGFR: estimated glomerular filtration rate,
HR: hazard ratio, CI: confidence interval.
* P value indicated a significant difference.

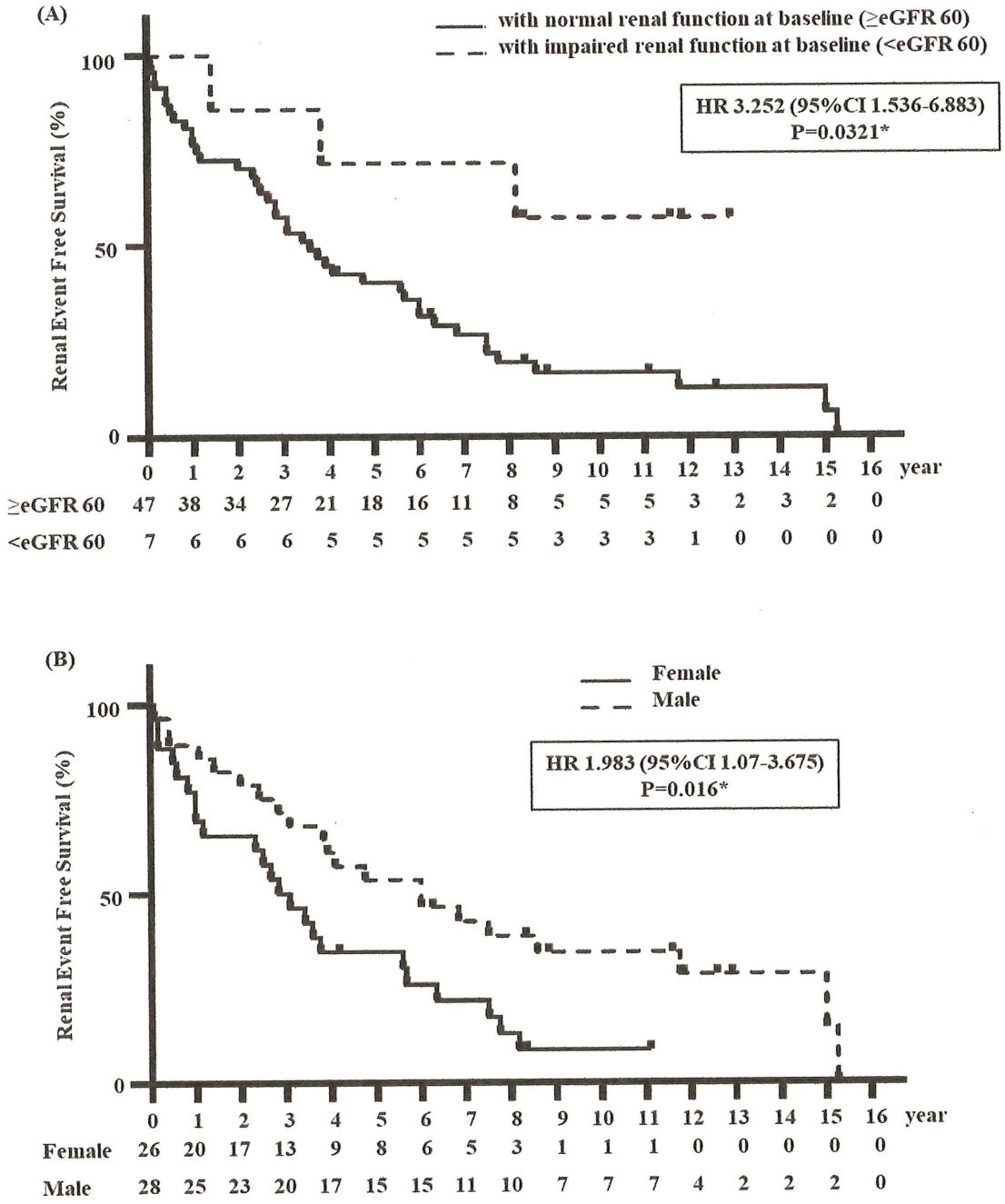


**Fig4.** Renal EFS in patients with first-line imatinib therapy.
(A) Renal EFS stratified by renal function at baseline.
Median survival was 3.58years (43 months) in with normal renal function at baseline (≥eGFR 60), not reached in patients with impaired renal function at baseline (<eGFR 60)
(B) Renal EFS stratified by gender.
Median survival was 2.96 years (35.5 months) in female, 6 years (72 months) in male.
EFS: Event Free Survival, eGFR: estimated glomerular filtration rate.
The data were statistically calculated with Log-rank (Mantel-Cox) test.
* p<0.05, * * p<0.01, * * * p<0.001, * * * * p<0. 0001.

Table 4. Univariate and Multivariate analysis on Renal EFS in patients with Imatinib therapy.

| Variables | Univariate analysis | | Multivate analysis | |
|---|---|---|---|---|
| | HR (95%CI) | P-Value | HR (95%CI) | P-Value |
| Normal renal function at baseline (eGFR≥60) | 3.356 (1.029-10.94) | 0.044* | 2.405 (0.6858-8.436) | 0.17 |
| Age <60 years | 1.776 (0.933-3.381) | 0.08 | 1.592 (0.764-3.318) | 0.213 |
| Female gender | 2.116 (1.13-3.965) | 0.019* | 2.24 (1.150-4.374) | 0.017* |
| No comorbidities | 1.578 (0.853-2.917) | 0.145 | 1.794 (0.936-3.438) | 0.078 |
| Dosage of Imatinib ≥400mg | 1.263 (0.683-2.333) | 0.455 | 0.99 (0.500-1.961) | 0.977 |

eGFR: estimated glomerular filtration rate, HR: hazard ratio; CI: confidence interval
* P value indicated a significant difference

Table 5. Mean dose of Imatinib therapy

| Characteristics | Imatinib mg/day | P value |
|---|---|---|
| Dosage of Imatinib | | <0.0001* |
| High (≥400mg /day) | 421.2 | |
| Low (<400mg /day) | 270.8 | |
| Gender | | 0.539 |
| Male | 312.2 | |
| Female | 347.6 | |
| eGFR at baseline | | 0.0886 |
| <60ml/min/1.73m$^2$ | 268 | |
| ≥60ml/min/1.73m$^2$ | 338.4 | |
| Mean eGFR reduction | | 0.6293 |
| ≥20ml/min/1.73m$^2$ | 334 | |
| <20ml/min/1.73m$^2$ | 308.6 | |

eGFR: estimated glomerular filtration rate
The data were statistically calculated with Mann-Whitney test .
* P value indicated a significant difference.